Remarks

Applicants' counsel thanks Examiner Lucas for his careful and thorough examination of the present application.

I. Formal Matters

Applicant continues to acknowledge that the Examiner has withdrawn the species elections with regard to Fraction A and Fraction C of Quillaja Saponaria Molina and that claims 3, 11, 16, 17, and 19 are withdrawn. Applicant notes again that claims 3 and 11 depend from claims 1 and 9, respectively. Accordingly, on allowance of claims 1 and 9, rejoinder and allowance of the claims 3 and 11 is respectfully requested pursuant to the Office's rejoinder procedure. MPEP § 821.04.

Applicant acknowledges that the Examiner has withdrawn the prior rejection of claims 8, 14, 22, and 23 under 35 U.S.C. § 112 for indefiniteness, has withdrawn the prior rejection of claims 1, 2, 6, 9, 10, 15, and 21 under 35 U.S.C. § 102(b) as being anticipated by the Wechter (U.S. Pat. No. 6,177,081), has withdrawn the prior rejection of claims 1, 2, 5-10, 13-15, and 20-23 under 35 U.S.C. § 103(a) as being unpatentable over Wechter in view of Morein (U.S. Pat. No. 5,679,354), and has withdrawn the rejection of claims 7, 8, 13, 14, 22, and 23 under 35 U.S.C. § 103(a) as being unpatentable over Wechter in view of Morein and further in view of Cox (WO 96/11711).

Claim 26 has been amended. No new matter has been added. Basis for the amendment can be found in the specification as filed. Specifically, the application discloses that a surprisingly high number of ferrets that received the live vaccine mixed with either of the two

iscom matrix adjuvants responded with higher titres than those receiving non-adjuvanted live vaccine. Para. [0117].

The Examiner has objected to claim 26 because it appears that the claim would more clearly describe the claimed invention by indicating that the composition provides for enhanced immunogenicity of the live micro-organism in a host. Applicants have amended claim 26 to indicate that the composition so provides for enhanced immunogenicity. Accordingly, the objection is respectfully submitted to be overcome.

II. Rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 under 35 U.S.C. § 103(a) over Van Woensel in combination with Morein

The Examiner has restated and maintained rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 under 35 U.S.C. § 103(a) as being unpatentable over Van Woensel et al. (U.S. Pat. No. 5,925,359) in combination with the teachings of Morein (U.S. Pat. No. 5,679,354). Respectfully, as explained in detail below, Van Woensel, in combination with Morein, does not make obvious a method of preparing an antigenic composition, comprising mixing an iscom particle and at least one live micro-organism, wherein the iscom particle is used as an adjuvant, as claimed in claim 1, or a composition comprising at least one iscom particle and at least one living micro-organism, as claimed in claim 9, respectively, because of at least the following three independently sufficient reasons:

(a) Van Woensel, in combination with Morein, would not have taught, suggested, or motivated one of ordinary skill to achieve the method of claim 1 or the composition of claim 9.

(b) Van Woensel, in combination with Morein, would not have provided one of ordinary skill with a reasonable expectation of success with regard to achieving the method of claim 1 or the composition of claim 9.

(c) The method of claim 1 and the composition of claim 9 provide unexpected results sufficient to overcome a prima facie case of obviousness.

I.a. Van Woensel, in combination with Morein, would not have taught, suggested, or motivated one of ordinary skill in the art to achieve the method of claim 1 or the composition of claim 9 because (i) Van Woensel, in view of the prior art, lacks credibility with regard to any general teaching, suggestion, or motivation that it may provide regarding including an adjuvant and a live micro-organism in a single composition for use as a vaccine and thus fails to teach, suggest, or motivate specifically including an iscom particle in such a composition, (ii) Morein does not contemplate use of an iscom particle with a live micro-organism and (iii) the combination of Van Woensel and Morein does nothing to cure their respective defects.

I.a.i. Van Woensel lacks credibility because any teaching, suggestion, or motivation that Van Woensel may provide regarding incorporation of an adjuvant into a live attenuated vaccine and regarding saponins as a suitable adjuvant conflicts with teachings or suggestions of authoritative references, already of record or submitted herewith, and with substantive declarations, also already of record or submitted herewith, that adjuvants in general and saponins in particular would not have been desirable for use in a single composition with a live micro-organism and because passages cited in Van Woensel do not include any experimental evidence or other persuasive support that might otherwise have resolved the conflict in Van Woensel's

favor. As stated in the MPEP, "[t]he test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings must be considered to the extent that they are in analogous arts." MPEP § 2143.01 (II). In this regard, "[w]here the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another." *Id.*

Van Woensel discloses that an adjuvant may be incorporated into a live attenuated vaccine, that suitable adjuvants include saponins, and that antigens may be incorporated into iscoms also as a possible way of adjuvation, specifically stating the following:

> An adjuvant and if desired one or more emulsifiers such as Tween and Span may also be incorporated in the live attenuated vaccine according to the invention. Suitable adjuvants are for example vitamin E acetate solubilisate, aluminium hydroxide, -phosphate or -oxide, (mineral) oil emulsions such as Bayol and Marcol52, and saponins. Incorporation of the antigens in Iscoms is also a possible way of adjuvation.

Van Woensel, col. 5, lines 12-19. As previously noted, Van Woensel does not specifically suggest the inclusion of the viruses in the same composition as an iscom. Office action dated August 6, 2009, at 5.

In conflict with Van Woensel's disclosure that an adjuvant may be incorporated into a live attenuated vaccine, numerous references of record or submitted herewith and substantive declarations of record teach or suggest that methods and compositions including an adjuvant and a live micro-organism in a single composition would not have been expected to be desirable or useful, for at least the reasons that an adjuvant is not necessary for generation of specific

immunity for a live attenuated vaccine and that adjuvants are known to have deleterious effects on hosts. Put another way, it had long been understood in the art that adjuvants are useful for improving the immunogenicity of killed vaccines, including sub-unit vaccines, because killed vaccines cannot establish a sub-clinical infection to provide long-lasting immunity and because their antigens tend not to be sufficiently immunogenic in the absence of an adjuvant for use as vaccines, and that such reasons have little or no applicability regarding live vaccines. It had also long been understood that the benefits associated with adjuvants must be weighed against the harm that they can cause a host. Accordingly, adding an adjuvant to a live vaccine would have been expected to cause net harm, and thus would not have been expected to be desirable or useful.

This understanding is supported, for example, by a reference to H.F. Stills, Jr., 46 ILAR Journal 280, 280 (2005), which is submitted herewith, which Applicants submit provides insights regarding understanding in the art at the time of invention, and which states the following:

> Adjuvants have been used for more that 70 yr to enhance the immune response of the host animal to an antigen . . . . The immunostimulatory properties of adjuvants result in inflammation, tissue destruction, and the potential for pain and distress in the host animal . . . . Balancing the requisite degree of immunostimulation and the extent of inflammation, necrosis, and potential pain and distress requires consideration of the nature of the antigen, the host immune responsiveness, the adjuvant's mechanisms of action, and the desired end-product. In cases where the antigen is a weak immunogen or has a very limited availability, the type and role of adjuvant becomes a critical component in producing an acceptable immune response and humoral antibody response.

This understanding is also supported by the reference Guideline on Adjuvants in Vaccines for Human Use, EMEA/CHMP/VEG/134716/2004, European Medicines Agency (20 January 2005), at 4-6, which is of record, which Applicants also submit provides insights regarding understanding in the art at the time of invention, and which states the following:

> Adjuvants should be chosen based on the type of immune response desired and should be formulated with the antigen in such a way that the optimal type of response with the minimal side effects is obtained . . . .
>
> The vaccines covered by this document are those that provide immunity against infectious diseases. Antigens may be in their native state, truncated or modified following introduction of mutations, detoxified by chemical or physical means and/or aggregated, polymerized or conjugated to a carrier (see also Ph.Eur. 04/2005:0153). So far, adjuvants have not been used in live vaccines for human use but this cannot be excluded in the future.

Similarly, the reference Note for Guidance on Pharmaceutical and Biological Aspects of Combined Vaccines, CPMP/BWP/477/97, European Medicines Agency (23 July 1998), at 7, which is also of record, states with respect to the use of an adjuvant in a combined vaccine that "[n]ew combined vaccines, except for live virus vaccines, may be proposed with new adjuvant compositions." This understanding is also supported by the reference I.G. Barr et al., 74 Immunology & Cell Biology 8, 8 (1996), which is also of record and which states "increasing use of highly purified proteins derived by recombinant DNA technology and synthetic antigens, most of which are poorly immunogenic, has increased the demand for alternative potent and predictable adjuvants."

The understanding regarding adjuvants is further supported by substantive declarations of the Inventor in the present case, Morein, and an Independent Expert, Fohlman, which are also of record and which state the following:

> Adjuvants are used in killed vaccines to enhance immunogenicity of the vaccine antigens. Killed vaccines, particularly subunit vaccines, are far less immunogenic and require the addition of an adjuvant to reach acceptable immunity compared to, for example, live attenuated vaccines that replicate in a controlled manner to give a subclinical infection stimulating long-lived immunity.

Morein Declaration dated May 18, 2009 (hereinafter "Morein Declaration I"), at para. 7; Fohlman Declaration dated June 15, 2009, at para. 8.

Also in conflict with Van Woensel, numerous references of record or submitted herewith and Morein Declaration I also teach or suggest that methods and compositions including a saponin, which as indicated above is one of the adjuvants disclosed by Van Woensel as a suitable adjuvant, and a live micro-organism in a single composition would not have been expected to be desirable or useful, for example because various saponins are known to have antimicrobial activities and thus saponins would be expected to have deleterious effects on a live micro-organism if included therewith in a single composition. For example, the reference S.G. Sparg et al. 94 Journal of Ethnopharmacology 219, 222-23, 235 (2004), which is of record, states that "[d]ue to their toxicity to various organisms, saponins can be utilised for their insecticidal, antibiotic, fungicidal, and pharmacological properties" and that "[s]aponins have also been reported to have antimicrobial activity," and provides several examples, citing references published in 1998 and 2002. Moreover, the reference G. Francis et al., 88 British Journal of Nutrition 587, 597 (2002), which is also of record, states that "[s]ome saponins and sapogenins

have been shown to be capable of deactivating viruses" and provides several additional examples. In addition, Morein has stated in the above-noted substantive declaration that "[s]aponins were known to have membrane-permeabilizing activity, indicating a negative effect on live organisms" and that "a person of ordinary skill in the art would not have been motivated to use saponins in any form together with live microorganisms." Morein Declaration I, para. 15.

With respect to this conflict, one of ordinary skill would give Van Woensel no weight relative to the numerous references and substantive declarations cited above, because, for example, the passages in Van Woensel cited by the Examiner, e.g. claim 8 and 16, column 5, lines 45-59, and column 5, lines 14-19, provide no experimental evidence or other support to show any beneficial effect associated with an adjuvant incorporated into a live attenuated vaccine, whereas the numerous references cited above correspond to scientific journal articles, each thoroughly supported by citations to the scientific literature, or to publications of the European Medicines Agency, a body of the EU that is authoritative based on its responsibility for scientific evaluation of applications for European marketing authorization for medicinal products, and the substantive declarations are supported based on, among other things, the credentials of the declarants and citations to the scientific literature.

Because Van Woensel conflicts with the numerous references and substantive declarations, and because one of ordinary skill would have given Van Woensel no weight relative to the references and declarations with regard to the desirability of incorporating adjuvants in general, and saponins in particular, in a live attenuated vaccine, the references and substantive declarations would have discredited Van Woensel in this regard. Accordingly, Van Woensel's disclosure that an adjuvant may be incorporated into a live attenuated vaccine, that suitable adjuvants include saponins, and that antigens may be incorporated into iscoms also as a

possible way of adjuvation would not have taught, suggested, or motivated one of ordinary skill to achieve a method or composition including an iscom particle in particular and a live micro-organism in a single composition, as claimed in claims 1 and 9.

I.a.ii. The Morein reference also would not have taught, suggested, or motivated including an iscom particle and a live micro-organism in a single composition. "All words in a claim must be considered in judging the patentability of that claim against the prior art." MPEP § 2143.03 (internal quotations omitted). As can be seen, claims 1 and 9 of the present application include the limitation of at least one live (or living) micro-organism. In contrast, to the extent that the Morein reference discusses including an iscom particle and a micro-organism in a single composition, Morein refers to a virus in general, not to a live virus in particular. Specifically, Morein states the following:

> As an example it can be mentioned that some viruses do not have amphipathic proteins, e.g. picornavirus, adenovirus or parvovirus, but they have a form of submicroscopic particle with the antigen presented in several copies, i.e. as multimers.
>
> For such viruses it is more practical to inject them together with the new adjuvant complex than to couple hydrophobic groups to them or create hydrophobic groups by other means (e.g. partial denaturation) and integrate them into an iscom particle.

Morein, col. 2, lines 33-42. As can be seen, this passage expressly refers to viruses, not live viruses, and thus does not include all of the limitations of claims 1 or 9. Moreover, there is nothing in Morein to suggest that live viruses were intended or would be useful. As indicated

above, one of ordinary skill would not have expected methods or compositions including an adjuvant and a live micro-organism in a single composition to have been desirable or useful, and thus, given the absence of a specific teaching about a live virus, would not have understood Morein's disclosure to be applicable to live viruses. Indeed, one of ordinary skill would have recognized that the viruses expressly disclosed in the cited passage, i.e. picornavirus, adenovirus, and parvovirus, are virulent viruses, and given the absence of a qualification regarding attenuation would have recognized that Morein was necessarily referring to killed virus. For comparison, see Example 4 of the Specification of present Application, which refers to "a commercial live vaccine (live attenuated vaccine against Canine Distemper, Adeno, Parvo and Parainfluenza virus)" (emphasis added). Consistent with this understanding, the Inventor of the present application, Morein, who of course is also an inventor of the Morein reference, has averred in the above-noted substantive declaration that "when the inventors of the '354 patent," i.e. the Morein reference, "including myself, indicated in the '354 patent that iscom matrix could be used as an adjuvant with whole organisms, we did not intend that Quillaja saponin and/or iscom matrix/iscom particles would be used with live whole microorganisms." Morein Declaration I, at para. 17. Although the Examiner states that "Morein further indicates that particulate compositions comprising saponins may be used as adjuvants by combining them with live viruses," cites for support Morein, column 2, lines 27-42, and characterizes the cited material as "specifically suggesting the use of a live virus not incorporated into the saponin containing adjuvant formulation," Office action dated August 6, 2009, at 5, for the reasons indicated above Morein nowhere suggests, specifically or otherwise, that the virus of the composition and use disclosed therein is a live virus or otherwise suggests the use of a live virus

in this regard. Accordingly, one of ordinary skill would not understand Morein to apply to live viruses.

I.a.iii. The combination of Van Woensel and Morein does nothing to cure their respective defects. Specifically, because Van Woensel lacks credibility with regard to any teaching, suggestion, or motivation that it may provide regarding including an adjuvant generally and a live micro-organism in a single composition for use as a vaccine, one of ordinary skill would not rely on Van Woensel in this regard as a basis for modifying the composition of Morein by including a live micro-organism. And because Morein does not contemplate use of an iscom particle with a live micro-organism, one of ordinary skill would not understand Morein to provide any credibility to Van Woensel with regard to including an adjuvant generally and a live micro-organism in a single composition, and thus would not have motivated one of ordinary skill to include an iscom particle in particular and a live micro-organism in a single composition. Accordingly, the combination of Van Woensel and Morein does nothing to cure their respective defects, and thus, for at least these reasons, Van Woensel in combination with Morein does not make obvious the method or composition of claims 1 or 9. Thus, the rejection of claims 1 and 9 is respectfully submitted to be overcome. Moreover, claims 2, 4, 10, 12, 15, 18, and 24-26 depend from claims 1 or 9, either directly or indirectly, and accordingly the rejection of these claims is also respectfully submitted to be overcome.

I.b. Van Woensel, in combination with Morein, would not have provided a reasonable expectation of success with regard to achieving the method of claim 1 or the composition of claim 9, for at least the reason that iscom particles were known to trigger multiple inflammatory

responses in a host, inflammatory responses were known to be potentially deleterious to a host and to a live micro-organism therein, and the bases of these responses with regard to iscoms were not understood and thus the extent and effect of these responses upon administration of an iscom particle and a live micro-organism in a single composition would not have been predictable to any degree.

Assuming, for purposes of argument only, that one of ordinary skill would have been motivated to combine Van Woensel and Morein to achieve the method and composition as claimed in claims 1 and 9, as explained in detail below, one of ordinary skill would not have had a reasonable expectation of success for the intended purpose of use as a vaccine, for at least the reason that iscom particles were known to trigger multiple, potentially deleterious, and poorly characterized inflammatory responses in a host, and the extent and effects thereof upon administration of an iscom particle and a live micro-organism in a single composition would not have been predictable. Accordingly, Van Woensel, in combination with Morein, would not have made obvious claims 1 or 9.

More specifically, as stated in the MPEP, "[o]bviousness does not require absolute predictability, however, at least some degree of predictability is required." MPEP § 2143.02, II. In this regard, "[e]vidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness." *Id.*

It was known in the art that iscom particles trigger multiple inflammatory responses in a host. The fact that iscom particles were known to trigger multiple inflammatory responses is shown, for example, in a reference to R.E. Smith et al., 162 Journal of Immunology 5536, 5536 (1999), which is submitted herewith and which states with regard to experiments in mice involving injection of iscoms including OVA protein that "[t]he i.p. injection of ISCOMS

induced intense local inflammation, with early recruitment of neutrophils and mast cells followed by macrophages, dendritic cells, and lymphocytes." The reference elaborates that although iscoms trigger multiple responses, only production of IL-12 appears to be of major importance with regard to generating antigen-specific immunity, stating the following:

> The results presented here indicate that ISCOMS induce intense local activation of the innate immune response, recruiting a wide variety of inflammatory cells, including neutrophils, mast cells, DC, Mϕ, and lymphocytes. Many of these cells are activated, as evidenced by the expression of surface activation markers and the production of cytokines and other mediators. However, the majority of these factors were not essential for the immunogenicity of ISCOMS in vivo, with only the production of immunoreactive IL-12 appearing to be of major importance.

Id. at 5541-42. Of note, this passage suggests that the non-IL-12 inflammatory responses induced by iscom particles may be extraneous based on being nonessential.

It was of course also known that inflammation can be highly detrimental to a host and to a live micro-organism therein, for example because inflammation can cause pain to the host and because inflammation is in part aimed at removing from the host an injurious stimuli such as the live micro-organism. Indeed, attenuated micro-organisms such as micro-organisms included in a live vaccine would be expected to be particularly susceptible to inflammation, as attenuated micro-organisms are specifically weakened with regard to their ability to maintain infection and thus are particularly susceptible to being killed, as demonstrated for example in a reference to a Nobivac Tricat Data Sheet,

http://www.intervet.co.uk/Products_Public/Nobivac_Tricat/090_Product_Datasheet.asp, which

corresponds to Exhibit A of the Morein Declaration submitted herewith (hereinafter "Morein Declaration II") and which highlights the extent to which the attenuated viruses in a live attenuated vaccine, specifically feline viral rhinotracheitis virus, feline calicivirus, and feline panleucopenia virus, are susceptible to killing. Specifically, the Nobivac Tricat Data Sheet states the following:

> The contents of one vial of reconstituted vaccine should be injected subcutaneously. Reconstitute immediately prior to use by the addition of the contents of one vial Nobivac Solvent, Nobivac FeLV or Nobivac Rabies. Sterile equipment should be used for administration. Avoid contamination of vaccine with traces of chemical sterilising agents. Do not use chemicals such as disinfectant or spiril to disinfect the skin prior to inoculation.

Id. The statements that the vaccine should be reconstituted immediately prior to use and that contamination with even traces of chemical sterilising agents should be avoided highlight the susceptibility of the live attenuated viruses to being killed, e.g. by prolonged storage after reconstitution and/or by chemicals. The above-noted iscom-mediated non-IL-12 inflammatory responses would have been of particular concern, given their risk of harming the host and the live micro-organism therein, with no expected concomitant benefit in terms of providing specific immunity.

The bases of iscom-triggered multiple inflammatory responses in general, and iscom-triggered IL-12 production in particular, were not understood. This is apparent, for example, from the Smith reference, which concludes as follows:

> [O]ur results show that the ability of ISCOMS to induce a wide range of Ag-specific immune responses [i.e. antigen-specific immune responses] is paralleled

> by the activation of a cascade of innate immune responses. This is consistent with other evidence that the best adjuvants are those that mimic the ability of pathogens to activate the innate immune system. However, our study also reveals the complexity of the resulting non-specific signals that are generated, with many overlapping and redundant mechanisms employed, only a few of which may play an essential role in the development of an Ag-specific immune response. Elucidating and targeting these mechanisms will be important in the design of a successful vaccine.

Id. at 5545. This is also evident from Smith's statement that "[t]he source of ISCOMS-induced IL-12 remains to be determined." *Id.* at 5544.

Because iscom particles were known to trigger multiple inflammatory responses, the responses were known to be potentially highly detrimental, and the bases of these iscom-mediated inflammatory responses were not understood, one of ordinary skill would not have had a reasonable expectation of success regarding achieving a method or composition including an iscom particle and a live micro-organism in a single composition, as claimed in claims 1 and 9. Put another way, although a live micro-organism and an iscom particle were both known to contribute to generation of specific immunity in different contexts, the result of combining the two in a single composition for use as a vaccine was not reasonably predictable. By way of illustration, starting at a high degree of specificity, IL-12 was understood to be important not just with regard to iscom-mediated adjuvation, as indicated above, but also with regard to infection of hosts by intracellular bacteria and with regard to tissue damage based on excessive inflammation. The latter two points are shown, for example, in a reference to Y. Zhan et al., 161 Journal of Immunology 1447, 1447 (1998), which is submitted herewith and which states that "[o]ne of the

early events in infection with intracellular bacteria is phagocytosis by resident macrophages and the release of cytokines by these cells," and that "[a] key role is played by IL-12, which up-regulates the production of IFN-γ by T cells and NK cells." Zhan teaches that i.v. infection of mice with the intracellular pathogen *Listeria monocytogenes* or the vaccine strain 19 of *Brucella abortus* results in detectable production of bioactive IL-12 followed by cessation of production of IL-12 while bacteria still persisted in high numbers. *See id.* at 1447-48, 1451. Zhan also teaches that "[t]hese experiments show that, in vivo, live but not killed *Listeria* and *Brucella* organisms triggered the secretion of detectable IL-12 bioactive protein" *Id.* at 1450. Zhan also notes that "[i]t has been said that IL-12 being a strongly inflammatory cytokine must be down-regulated before tissue damage occurs." *Id.* at 1451. Accordingly, Zhan, in view of Smith, suggests that careful control of IL-12, not just in terms of production but also in terms of cessation of production, would have been a crucial factor for achieving success in the development and use of a vaccine including an iscom particle and live micro-organism. However, it would not have been apparent from these references whether the effect of an iscom particle and a live micro-organism on IL-12 production would have been e.g., additive, synergistic, less than the sum of the parts, or something else entirely, and further the effect of the resulting IL-12 production on the host and the live micro-organism therein would also not have been apparent. It also would not have been apparent from these references whether and to what extent IL-12 levels might become excessively high based on induction by both an iscom particle and live micro-organism, and/or whether and to what extent cessation of production of IL-12 might be affected, and again how this might affect the host and live micro-organism therein. Accordingly, there would not have been any degree of predictability regarding how administration of a single composition including both an iscom particle and an intracellular

bacterium might affect IL-12 production, and thus the desirability and usefulness of the composition as a vaccine also would not have been reasonably predictable.

Now considering the issue more broadly, this concern would also have been applicable regarding not just intracellular bacteria but other micro-organisms too because induction of IL-12 production had been shown to be important for pathogenicity in other micro-organisms, as shown for example in a reference to M.S. Di Genaro, 71 Infection & Immunity 1804, 1804-05 (2003), which indicates that IL-12 is essential for clearance of infections of *Yersinia enterocolitica*, a gram-negative, extracellularly located pathogen. The above-noted lack of predictability would also have been compounded upon consideration of the above-noted fact that iscom particles were also known to induce multiple additional and potentially deleterious inflammatory responses, the bases of each of which, again as indicated above, were not understood.

For at least the reasons above, one of ordinary skill would not have recognized any degree of predictability with regard to a method or composition including an iscom particle and a live micro-organism in a single composition for its intended use, namely as a vaccine. Accordingly, for at least these additional reasons, Van Woensel, in combination with Morein, does not make obvious the method or composition of claims 1 or 9. Thus, the rejection of claims 1 and 9 is respectfully submitted to be overcome. Moreover, claims 2, 4, 10, 12, 15, 18, and 24-26 depend from claims 1 or 9, either directly or indirectly, and accordingly the rejection of these claims is also respectfully submitted to be overcome.

I.c. Use of compositions including an iscom particle and a live micro-organism as live attenuated vaccines provides unexpected results in terms of not decreasing replication of the live

micro-organism and of increasing the antibody titer against the live micro-organism, and thus Van Woensel, in combination with Morein, does not make obvious the claimed methods or compositions.

Assuming, for purposes of argument only, that one of ordinary skill would have been motivated to combine Van Woensel and Morein and would have had a reasonable expectation of success, the method and composition as claimed in claims 1 and 9 still would not have been obvious because the use of a composition including an iscom particle and live micro-organism as a vaccine provides a greater than expected result in terms of not decreasing replication of the micro-organism and in terms of increasing antibody titer against the live micro-organism. Accordingly for at least these additional reasons, Van Woensel, in combination with Morein, would not have made obvious claims 1 or 9.

More specifically, "[a] greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness . . . of the claims at issue." MPEP § 716.02(a)(I).

The method and composition of claims 1 and 9, including an iscom particle and a live micro-organism in a single composition, provide a greater than expected result in terms of not decreasing replication of a live micro-organism. Specifically, as disclosed in detail in the Specification, Example 2, the Applicants have demonstrated with experimental data that "none of the matrix or iscom formulations mentioned above reduced the EID50 titres [i.e. the end point where 50% of the embryos are infected] compared to the control groups," and that "[i]n contrast oil and aluminum hydroxide reduced the EID50 titres more than a 10 log." In these experiments, the Applicants had tested the effects of various adjuvants, including various iscom and iscom matrix preparations, as well as oil and aluminum hydroxide, on replication of influenza virus in chicken embryos. The results were greater than expected, for at least the reasons that iscom

particles include saponins and various saponins were known to have anti-microbial activities, as discussed above, and thus it would have been expected that mixing iscom particles and the influenza virus in a single composition would have resulted in a decreasing replication of the live micro-organism relative to the absence of iscom particles. Of note, the results surprisingly indicate that "matrix formulations are 'compatible' for use in vaccines, which contain live micro-organisms," whereas oil and aluminum hydroxide are not.

Moreover, as also disclosed in detail in the Specification, Example 3, the Applicants have demonstrated with experimental data that "A-matrix, C-matrix treated virus titered both out to 5.7 i.e. a ten fold higher titre than the virus control i.e. an un-expected increase in virus growth." Moreover, the Applicants demonstrated that "703 matrix (4.7), A+C-matrix (4.7), Q-VAC matrix (4.5), free saponin A, influenza virus Iscoms (4.9) and bovine respiratory syncytial virus Iscoms (4.4)" exhibited titres that "did not significantly differ from the titres of the virus control." *Id.* In contrast, "Spikoside matrix, free saponin C, free 703 and free spikoside, oil adjuvant and aluminumhydroxide decreased more than a ten fold the virus titres compared to the virus control." In these experiments, the Applicants had tested the effects of various adjuvant formulations on virus titres in cell culture. *Id.*. The results were greater than expected, for the reasons indicated above regarding Example 2. Again, the results surprisingly indicate that various iscom and iscom matrix preparations are compatible for use in live vaccines. *Id.*

The method and composition of claims 1 and 9, including an iscom particle and live micro-organism in a single composition, also provide a greater than expected result in terms of increasing titres of antibodies to live vaccine components included in a vaccine. Specifically, as disclosed in detail in the Specification, Example 4 and Tables 2-4, the Applicants have demonstrated with experimental data that serum antibody responses were higher against both live

antigens and against the killed rabies virus vaccine antigen in the animals immunized with vaccine supplemented with MM703 and MB703 formulations than in the control group that was immunized with non-adjuvanted vaccine. In these experiments the Applicants had tested antibody titres based on ELISA assays in ferrets that had been vaccinated with a commercial live vaccine corresponding to Canine Distemper, Adeno, Parvo, and Parainfluenza virus, mixed with purified killed rabies virus component (control) or the same adjuvanted with either of two different iscom matrix preparations. Assuming for purposes of argument only that one of ordinary skill would have had a reasonable expectation of success with regard to use as a vaccine, the results were greater than expected given that, as indicated above, attenuated viruses were known to be particularly susceptible to being killed, e.g. by chemicals, iscom particles include saponins, various saponins are known to have anti-microbial activities, but nonetheless the iscom matrix preparations did not apparently harm the attenuated viruses but rather led to an increase in their effectiveness at triggering the generation of antibodies. The results were also greater than expected in view of the understanding in the art, as discussed above, that an adjuvant is not necessary for generation of specific immunity for a live attenuated vaccine and that adjuvants are known to have deleterious effects on hosts. The results indicate that various iscom matrix preparations would be desirable for use in live vaccines. *Id.*

Moreover, as indicated in the Morein Declaration II submitted herewith, a greater than expected result in terms of increasing titres of antibodies to live vaccine components included in a vaccine was also observed with respect to additional live viruses in an additional host animal. Specifically, the Applicants have demonstrated with experimental data that the antibody responses were higher in the animals immunized with vaccine supplemented with iscom matrix MM703 including 83% of Fraction A and 17% of Fraction C of Quil A than in the control group

that was immunized with non-adjuvanted vaccine. In the experiments the Applicants had tested antibody titres based on vaccination of cats once with Nobivac Tricat formulation, a live attenuated vaccine including feline viral rhinotracheitis virus, feline calicivirus, and feline paneleucopenia virus, as described above, and had observed, upon measuring antibody titres at fourteen days after vaccination, that for all three viruses tested the antibody response was higher when the live attenuated viruses were administered together with iscom matrix, as indicated in Exhibit B of Morein Declaration II, submitted herewith. Again, for the reasons indicated above the results were greater than expected. Also again, the results indicate that various iscom matrix preparations would be desirable for use in live vaccines.

Thus, for at least the additional reasons above, the combination of Van Woensel and Morein does not make obvious the inventions as claimed in claims 1 and 9. Again, for these additional reasons, the rejection of claims 1 and 9 is respectfully submitted to be overcome. Moreover, claims 2, 4, 10, 12, 15, 18, and 24-26 depend from claims 1 or 9, either directly or indirectly, and accordingly the rejection of these claims is also respectfully submitted to be overcome.

III. Rejection of claims 5-8, 13, 14, and 20-23 under 35 U.S.C. § 103(a) over Van Woensel and Morein and further in combination with Cox

The Examiner has restated and maintained rejection of claims 5-8, 13, 14, and 20-23 under 35 U.S.C. § 103(a) as being unpatentable over Van Woensel and Morein, and further in combination with Cox (WO 96/11711). Respectfully, for at least the reasons provided above, Van Woensel in combination with Morein does not teach, suggest, or motivate a method or composition including an iscom particle and a live micro-organism in a single composition, as

claimed, or provide a reasonable expectation of success, and the passages cited in Cox do nothing to cure the defects of Morein and Van Woensel in this regard or to provide a reasonable expectation of success. Specifically, the Examiner has asserted that "Cox teaches that iscoms may be in the forms of iscoms comprising the glycosides and lipids identified in the rejected claims," "that iscom matrices may be used which incorporate an immunogen," and that "preferred embodiments of such iscoms use as glycosides Fractions A and C of Quil A." Office action dated July 28, 2008. As can be seen, the asserted teachings are not directed to including an iscom particle and a live micro-organism in a single composition. Thus, Van Woensel and Morein, further in combination with Cox, does not make obvious the inventions as claimed in claims 5-8, 13, 14, and 20-23. The rejection of claims 5-8, 13, 14, and 20-23 is therefore respectfully submitted to be overcome.

IV. Citation of Haanes as pertinent to Applicants' disclosure

The Examiner states that Haanes (U.S. Pat. No. 5,753,235) is considered pertinent to Applicants' disclosure. Respectfully, Haanes is not pertinent to Applicants' disclosure, because, for reasons similar to those provided above regarding Van Woensel, Haanes lacks authority with regard to any potential teaching, suggestion, or motivation that it might arguably be understood to make in the absence of other prior art. Moreover, Haanes teaches away from a composition including a live virus and an iscom particle, by expressly stating that "[o]ne advantage of live virus-based vaccines, such as the recombinant CHVs of the present invention, is that adjuvants and carriers are not required to produce an efficacious vaccine, and in some cases, the advantages of recombinant CHV vaccines of the present invention would be precluded by the use of some adjuvants," col. 29, lines 26-33, providing a list of "suitable adjuvants" that does not

specifically include iscom particles, col. 29, lines 36-45, and nowhere else mentioning iscom particles. For at least these reasons, Haanes is not pertinent to Applicants' disclosure.

V. Request for reconsideration and notice of allowance

Applicants respectfully submit that all of the presently pending, non-withdrawn claims are allowable for at least the reasons set forth above. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections and request notice that the application is in condition for allowance.

If there are any additional fees resulting from this communication, please charge the same to our Deposit Account No. 16-0820, our Order No. ALBI-41848.

Respectfully submitted,
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